

REMARKS

The present application is directed to a method for performing a nucleic acid amplification reaction. An apparatus for effecting the method as well as disposable units for use in the method are disclosed. Claims 1-35 were pending prior to the issuance of the October 6, 2004, Office Action. Following entry of this amendment, Claims 1-6 and 8-35 will be pending. Claims 1, 2-3, 5, 10-11, 13, 16, 19-22, 24, 27 and 29-30 are amended and Claim 7 is cancelled. No new matter is added, and support for the amendments is found throughout the specification and in the original claims.

Sequence Listing

Applicants respectfully request that the attached Sequence Listing (page 1) be added behind the Abstract of the application. This Sequence Listing is a substitute paper copy which comprises the nucleotide and/or amino acid sequences contained in the application as originally filed. Applicants also submit a substitute Computer Readable Form of the Sequence Listing. Pursuant to 37 C.F.R. § 1.821(e) and (f), the Sequence Listing contained in the paper copy as well as the Computer Readable Form contains no new subject and the paper copy and the Computer Readable Form are the same.

Claim objections.

In the October 6, 2004 Office Action, the Examiner objected to use of the symbol “@” in Claim 5 and suggested that the symbol be replaced with the word “at”. Applicants have replaced the symbol as suggested by the Examiner.

The Examiner objected to the use of the term “heat sealed” in Claim 13 and suggested that it be replaced with the term “heat-sealed” to avoid confusion. Applicants have replaced the term as suggested by the Examiner.

The Examiner objected to Claim 16 for not further defining the method step and suggested alternative language. Applicants have amended Claim 16 in accordance with the Examiner’s suggestion.

Accordingly, Applicants respectfully submit they have overcome the Examiner’s objections.

Rejections under 35 U.S.C. §112, second paragraph

In the October 6, 2004 Office Action, the Examiner rejected Claims 1-27 under 35 U.S.C. §112, second paragraph, for failing to particularly point out and claim the subject matter that Applicants regard as the invention. Applicants respectfully submit that the amendments to the claims overcome the rejection.

Applicants have amended Claim 1 to clarify that a **reaction mixture** in a **reagent** well comprises the recited components.

The Examiner rejected Claim 2 for not further limiting the parent claim. Applicants have amended Claim 2 to specify a pH that is higher than the pH specified in Claim 1.

The Examiner rejected Claim 5 for failing to establish proper antecedent basis. Applicants have amended claim 5 to depend from Claim 4.

Claim 7 was rejected by the Examiner as indefinite on the basis that trademarked goods were mentioned. Applicants respectfully submit that the use of trademarked terms in claims is permissible. However, in order to expedite prosecution, Claim 7 has been cancelled.

The Examiner rejected Claims 10-12, for lacking antecedent basis for the term “the thermally conducting metal layer”. Applicants have amended Claims 10-12 to depend from Claim 9, which contains the term.

The Examiner rejected Claim 20, for lacking antecedent basis. Applicant have amended Claim 20 to depend from Claim 19.

The Examiner rejected Claim 22 as being an improper multiple dependent claim. Applicants have amended Claim 22 to remove the reference to “preceding claims”. Claim 22 is now solely dependent on amended Claim 1.

The Examiner rejected Claim 24 as indefinite for reciting “the heating block” on the basis that Claim 22 recites “at least two heating blocks”. Claim 24 depends from Claim 22. Applicants have amended Claim 24 to clarify that “at least one of the heating blocks” is segregated.

Accordingly, Applicants respectfully submit they have overcome the Examiner’s rejections under 35 U.S.C. §112, second paragraph, and request the withdrawal thereof.

Rejections under 35 U.S.C. §102

In the October 6, 2004 Office Action, the Examiner rejected Claims 1, 2, 4, 6, 7, 25 and 26 under 35 U.S.C. §102(b) as anticipated by Innis *et al.*, (U.S. Patent No. 5,075,216). Applicants respectfully traverse the Examiner’s rejection.

Innis *et al.* describe a method for DNA **sequencing**, not DNA **amplification**. The sequencing method described by Innis *et al.* involves template-dependent extension of an oligonucleotide primer annealed to the nucleic acid to be sequenced. Innis *et al.* fail to disclose a method for performing an amplifying reaction as recited in Claim 1. In particular, Innis *et al.* fail to teach amplification of a target nucleic acid sequence, because **no thermal cycling is conducted**. In contrast, Claim 1 of the present application requires that a disposable unit be subjected to thermally cycling conditions to amplify a target nucleic acid sequence.

Furthermore, Claim 1 of the present application specifies that a disposable unit comprising a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth is used to carry out the amplification reaction. Innis *et al.* fail to disclose a disposable unit and instead utilize conventional 0.5 ml microcentrifuge tubes (see column 12, lines 60-61).

The Examiner rejected Claims 1, 4 and 8 under 35 U.S.C. §102(b) as anticipated by Hartley (U.S. Patent No. 5,043,272). Applicants respectfully traverse the Examiner's rejection.

Hartley describes a method for amplifying nucleic acid sequences in which random primers are utilized. Hartley's method was devised to circumvent several disadvantages associated with the PCR (see column 1, line 66-column 2, line 17), one disadvantage being that PCR requires sophisticated programmable equipment to perform the method in which multiple heating and cooling cycles are required (see column 2, lines 10-17). Thus, Hartley **teaches away** from the use of thermal cycling to amplify a target nucleic acid sequence (see column 9, lines 10-13). In contrast, Claim 1 of the present application requires that a reaction mixture be subjected to thermally cycling conditions to amplify the target nucleic acid sequence.

The Examiner rejected Claims 29-31 and 33 under 35 U.S.C. §102(e) as anticipated by Foote (U.S. Patent No. 5,944,971) on the basis that Foote discloses a disposable unit with a thermally conducting layer and a facing layer having a plurality of reagent wells defined therebetween, wherein all wells are fed by a common channel. The Examiner further stated that Foote disclose that the disposable unit has probe/primer oligonucleotides immobilized therein and thus anticipates Claims 30 and 31. The Examiner concluded that Foote also disclose a method of filling disposable units with reagents or wash solutions, rendering Claim 33 anticipated. Applicants respectfully traverse the Examiner's rejection.

Claim 29 of the present application specifies that the reagent wells are fed by a common channel which includes **a single opening** to the outside of the unit. In contrast, Foote discloses a channel in which **ends** are connected to fluid reservoirs (see column 6, lines 66-67). It is inherent from the use of the plural term "ends" that the microchip of Foote has more than one opening. In addition, Foote discloses embodiments where more than one manifold channel is present, with both ends being open (see column 7, lines 8-10). Furthermore, Foote disclose an embodiment in which the cover plate is provided with access **ports** (column 7, lines 16-20). Therefore, the unit described by Foote has **multiple openings**, not a single opening as specified in Claim 29. Such a feature is not trivial. For example, a disposable unit having only one opening, as claimed, allows simplification of the filling operation and minimizes the risk of contamination (see page 8, line 8-11 of the instant application).

For at least the above reasons, Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §102(b) and request withdrawal thereof.

Rejections under 35 U.S.C. §103

In the October 6, 2004 Office Action, the Examiner rejected Claims 3 and 8 under 35 U.S.C. §103(a) as unpatentable over Innis *et al.* (U.S. Patent No. 5,075,216), in view of Hartley (U.S. Patent No. 5,043,272) and Cheng (U.S. Patent No. 5,512,462). The Examiner stated that Innis *et al.* disclose a method of amplifying a target nucleic acid molecule, but do not teach a blocking agent such as bovine serum albumin (BSA) or a buffer system having a pH range of 8.7-9.0. However, the Examiner asserted that Hartley discloses use of BSA and that Cheng discloses an amplification method using a buffer having pH 8.7. Applicants respectfully traverse the Examiner's rejection.

As explained above, Innis *et al.* describe a method for DNA sequencing, not DNA amplification. In addition, Innis *et al.* fail to teach amplification of a target nucleic acid sequence, because no thermal cycling is conducted. Furthermore, Innis *et al.* fail to disclose a disposable unit, and instead utilize conventional 0.5ml microcentrifuge tubes (see column 12, lines 60-61).

The deficiencies of Innis *et al.* are not satisfied by Hartley for at least the following reasons. The method disclosed by Hartley **teaches away** from the use of thermal cycling to amplify the target nucleic acid sequence (see column 9, lines 10-13). Moreover, Hartley utilizes conventional PCR tubes instead of a disposable unit as claimed in the present application (see column 10, lines 19-21).

The deficiencies of both Innis *et al.* and Hartley are not satisfied by Cheng for at least the following reasons. Cheng fails to disclose a disposable unit comprising a thermally conducting

layer and a facing layer having one or more reagent wells of up to 1000 microns in depth and instead utilizes MicroAmpTM tubes with individual caps (see column 18, lines 36-39).

For at least the foregoing reasons, applicants respectfully submit that the cited references, alone or in combination, fail to describe all of the elements of the claimed method. Therefore, applicants request withdrawal of the rejection under 35 U.S.C. §103(a).

The Examiner rejected Claim 5 under 35 U.S.C. §103(a) as being unpatentable over Innis *et al.* (U.S. Patent No. 5,075,216), in view of Hartley (U.S. Patent No. 5,043,272) and Cheng (U.S. Patent No. 5,512,462) as applied to Claims 3 and 8 above, and further in view of Burckhardt (U.S. Patent No. 5,501,963). Applicants respectfully traverse the Examiner's rejection.

As explained above, Innis *et al.*, Hartley and Cheng fail to teach a method for DNA amplification in which a disposable unit comprising a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth is employed.

The deficiencies of Innis *et al.*, Hartley and Cheng are not satisfied by Burckhardt for at least the following reasons. Burckhardt utilize conventional PCR tubes and therefore fail to disclose a disposable unit as claimed in the present application.

For at least the foregoing reasons, applicants respectfully submit that the cited references, alone or in combination, fail to describe all of the elements of the claimed method. Therefore, applicants request withdrawal of the rejection under 35 U.S.C. §103(a).

The Examiner rejected Claims 13-16, 18 and 27 under 35 U.S.C. §103(a) as unpatentable over Innis *et al.* (U.S. Patent No. 5,075,216) in view of Kris *et al.* (U.S. Patent No. 6,238,869) on the basis that microtiter plates are known in the art of amplification and that, although Kris *et al.*

do not explicitly disclose the microtiter plate as thermally conductive, the make up of the microtiter plate of Kris *et al.* would conduct heat and allow thermocycling to occur. Applicants respectfully traverse the Examiner's rejection.

Kris *et al.* fail to satisfy the deficiencies of Innis *et al.* for at least the following reasons. The present application requires a disposable unit comprising a thermally conducting layer and a **facing layer** having one or more reagent wells of up to 1000 microns in depth, to carry out the amplification reaction of Claim 1. Kris *et al.* fail to suggest or disclose a microtiter plate containing a facing layer.

Furthermore, Kris *et al.* teaches use of microtiter plates as supports for multiple high throughput chemical or biochemical assays, where reagents need to be added to wells during processing or repeatedly utilized (see column 2, lines 51-55). Applicants respectfully submit that the insertion of a facing layer, as recited in the instant claims, would impede the intended function of the microtiter plates of Kris *et al.* Therefore, one skilled in the art would lack the motivation to modify the microtiter plates to include a facing layer.

For at least the foregoing reasons, applicants respectfully submit that the cited references, alone or in combination, fail to describe all of the elements of the claimed method. Therefore, applicants request withdrawal of the rejection under 35 U.S.C. §103(a).

The Examiner rejected Claims 19 and 20 under 35 U.S.C. §103(a) as unpatentable over Innis *et al.* (U.S. Patent No. 5,075,216) in view of Little *et al.* (U.S. Patent No. 6,077,669) on the basis that Little *et al.* disclose a well known method of providing reagents in a dried form in a disposable device. Applicants respectfully traverse the Examiner's rejection.

The deficiencies of Innis *et al.* as described above are not satisfied by Little *et al.* The method disclosed by Little *et al.* fails to teach a disposable unit comprising a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth, to carry out the amplification reaction as claimed in Claim 1. Claims 19 and 20 depend from Claim 1 and contain all the limitations thereof. Therefore, Claims 19 and 20 are also non-obvious.

For at least the foregoing reasons, applicants respectfully submit that the cited references, alone or in combination, fail to describe all of the elements of the claimed method. Therefore, applicants request withdrawal of the rejection under 35 U.S.C. §103(a).

The Examiner rejected Claims 22-24 under 35 U.S.C. §103(a) as unpatentable over Innis *et al.* (U.S. Patent No. 5,075,216), in view of Danssaert *et al.* (U.S. Patent No. 5,525,300) on the basis that Danssaert *et al.* disclose an apparatus containing multiple heating blocks. Applicants respectfully traverse the Examiner's rejection.

The deficiencies of Innis *et al.* are not satisfied by Danssaert *et al.* for at least the following reasons. The method disclosed by Danssaert *et al.* fails to disclose a reaction mixture containing a buffer system having a pH above 8.3, a detergent, a blocking agent, or a combination thereof as recited in Claim 1.

It is to Applicants' credit that they successfully devised a disposable unit having a thermally conducting layer and shallow wells and unexpectedly discovered that the act of subjecting the disposable unit to thermal cycling results in a faster PCR reaction than conventional methods in conventional tubes. Applicants further discovered that when certain conditions were applied to the PCR reaction, namely the presence of a buffer system having a pH

above 8.3, a detergent, or a blocking agent, the reaction worked more effectively. These conditions are recited in Claim 1 of the present application and are not taught by the cited references. Claims 22-24 depend from Claim 1 and contain all the limitations thereof.

For at least the foregoing reasons, applicants respectfully submit that the cited references, alone or in combination, fail to describe all of the elements of the claimed method. Therefore, applicants request withdrawal of the rejections under 35 U.S.C. §103(a).

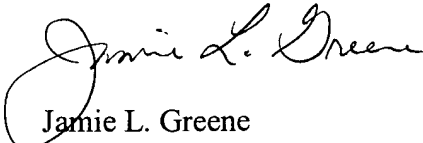
CONCLUSION

The foregoing is submitted as a full and complete Response to the Office Action mailed on October 6, 2004. For at least the reasons given above, Applicants respectfully submit that the pending claims are definite, novel and non-obvious. Accordingly, Applicants submit that the claims in the present application are in condition for allowance, and such action is courteously solicited.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 11-0855.

If the Examiner believes that any informalities remain in the case, which may be corrected by Examiner's amendment, or that there are any other issues which can be resolved by a telephone interview, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully solicited.

Respectfully submitted,



Jamie L. Greene
Reg. No. 32,467

KILPATRICK STOCKTON LLP
1100 Peachtree Street, Suite 2800
Atlanta, Georgia 30309
Telephone: 404-815-6500
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